REMARKS

Claims 1, 6-10, 15, 18, 20, 22, and 31, appear in this amendment for the Examiner's review and consideration. Claims 1, 6, 15 and 31 have been amended to recite only the elected invention. Accordingly, claims 4-5, 11-14, 17, 19, 21, 23-30, 36-37 and 45-49 have been cancelled. Claims 31, 32, 38, 43 and 44 have been amended for clarity. The specification has been amended to correct informalities. As no new matter is introduced by these changes, the entry of these amendments is warranted at this time.

Applicants respectfully submit that the priority data of US provisional application 60/299,187 should be honored because it discloses the same invention as the PCT/IL02/00494 application. It is respectfully submitted that the written description requirement and enabling requirement are irrelevant to priority data.

The Examiner erred in objecting to the drawings for failure to mention the reference characters 9B, 9C, 16B, 16C, 16D and 16E. As a matter of fact, these reference characters are clearly disclosed in the specification. In particular, paragraph [0074] of the published application recites "FIGS. 9A-9D" which includes figures 9B and 9C while paragraph [0081] of the published application recites "FIGS. 16A-16F" which includes figures 16B, 16C, 16D and 16E. Thus, the objection to the drawings should be withdrawn.

The specification is objected to because of the use of improperly demarcated trademarks. In response, Applicants have amended the specification to show the marks in capital letters to correct these informalities. Thus, the objection is overcome and should be withdrawn.

Regarding the Brief Description of the Drawings, the Examiner erred in stating that the description of "Figure 9 does not specifically refer to Figure 9B and 9C and the description of Figure 16 does not specifically refer to Figure 16B, 16C, 16D and 16E". As explained above, paragraph [0074] of the published application recites "FIGS. 9A-9D" which includes figures 9B and 9C while paragraph [0081] of the published application recites "FIGS. 16A-16F" which includes figures 16B, 16C, 16D and 16E. Thus, the objection to the Brief Description of the Drawings should be withdrawn.

Claims 4, 7 and 8 are objected to as being drawn in the alternative to the subject of non-elected inventions. In response, claim4 has been cancelled. Regarding claims 7 and 8, Applicants respectfully point out that all V_H and V_L combinations in claims 7 and 8 are drawn to

the elected invention even though only one pair in each claim is designated as the elected species. Thus, the objection is overcome and should be withdrawn.

Claims 1, 4-10, 15, 17, 22 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleges that the recitation of "antibody which has increased affinity for a fibroblast growth factor receptor" in claim 1 is indefinite. Applicants respectfully disagree. Paragraph [0135] of the published application clearly defines the meaning of "increased affinity" as follows: "(a)n antibody or a molecule of the present invention is said to have increased affinity for a RPTK if it binds a soluble dimeric form of said RPTK with a K_D of less than about 50 nM, preferably less than about 30 nM and more preferably less than about 10 nM, as determined by the BIACORE^{TM} chip assay for affinity, by a FACS-Scatchard analysis or other methods known in the art." (emphasis added).

The Examiner also alleges that the terms "fibroblast growth factor receptor" in claim 1 and "FGFR3" in claim 4 are indefinite. In response, Applicants have amended claim 1 to recite FGFR3 and cancelled claim 4. Applicants respectfully point out that the reciatation "FGFR3" is definite. First, paragraph [0013] of the published application clearly points out with the requisite particularity the identity of the claimed proteins, reciting that FGFRs "consist of an extracellular ligand binding domain, a single transmembrane domain and an intracellular tyrosine kinase domain which undergoes phosphorylation upon binding of FGF. The FGF receptor (FGFR) extracellular region contains three immunoglobulin-like (Ig-like) loops or domains (D1, D2 and D3), an acidic box, and a heparin binding domain. Five FGFR genes that encode for multiple receptor protein variants have been identified to date." Second, although the Examiner is correct in noting the differences among different FGF receptors, it should be emphasized that they are classified as a protein family because they share striking similarities both structurally and functionally. In particular, as cited above, the extracellular region of FGFR, where the antibodies of the present invention bind, contains the same Ig-like domains (D1, D2 and D3), an acidic box, and a heparin binding domain. Thus, there is sufficient structural similarities among the members of FGFR family to make the recitation "FGFR3" definite.

Regarding the recitation that the "molecule blocks constitutive activation" in claims 6-10, the Examiner is correct in stating that a constitutively active receptor is a receptor that has been modified such that it is always active. However, it is Applicants' surprising finding that even the

activity of these ligand-independent, constitutively active receptors can be blocked by molecules of the present invention. Thus, the meaning of the claim language "molecule blocks constitutive activation" is clear and definitive, as known in the art.

Claims 1, 4-6, 8-10, 15, 17, 22 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. In response, Applicants respectfully point out that claims 1, 4-6, 8-10, 15, 17, 22 and 31 are drawn to a structurally and functionally defined molecules comprising the antigen-binding portion of an isolated antibody which has an increased affinity for a fibroblast growth factor receptor such as FGFR3 and which blocks activation of said fibroblast growth factor receptor. Moreover, the present invention provides more than twenty examples of such molecules (e.g. Table 1F of the present application), which unequivocally demonstrate that Applicants are in possession of the claimed invention. Furthermore, Applicants also provide detailed description of the screening process so that more molecules of the present invention can be isolated.

The Examiner's concern that a similar structure in proteins does not always mean a similar function is not without foundation. However, the exceptions that have been reported are strikingly few comparing to the vast majority of the cases where the structural-functional correlation hold true. A prudent skilled person in the art will inevitably associate like structures with like functions while keeping an open mind for exceptions. It is inconceivable that anyone skilled in the art will choose to ignore the enormous amount of confirmed scientific information regarding structural-functional correlation of proteins, even though everyone in the art is aware of exceptions.

The Examiner is correct that different constitutive FGFR3 receptors have different mutations. However, molecules of the present invention are capable of blocking the function of these receptors regardless where the mutation is located in the FGFR3 receptor. Thus, there is no need to distinguish different kinds of FGFR3 mutations.

The Examiner is also correct in suggesting that the activities of the constitutive FGFRs and the ligand–dependent FGFRs are blocked by different antibodies, which is exactly what is disclosed in the application. In particular, the molecules recited in claims 7 and 8 that block the constitutive active FGFRs are different from those recited in claims 18 and 20 which block the activity of ligand–dependent FGFRs.

Regarding to the Examiner's comments on CDR3 region, Applicants respectfully submit that the specification provides clear guidance for one skilled in the art to use the CDR3 regions by grafting (see paragraph [0149] of the published application). Thus, there is no need to discloses the other four CDR regions (CDR1 and CDR2 of the heavy chain and light chain).

In summary, the rejection under 35 U.S.C. § 112, first paragraph, as lacking adequate written description is overcome and should be withdrawn.

Claims 1, 4-6, 8-10, 15, 17, 22 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. First, in response to the Examiner's allegation that "the specification does not provide any specific non-general guidance that would allow one of skill in the art to make antibodies that block the constitutive activation of FGFR3 polypeptides with mutations that result in receptors with constitutive kinase activity, such as the fibroblast growth factor receptor 3 polypeptide with a Glycine 380 to Arginine substitution", it is respectfully submitted that Examples 1-5 provide step by step guidance for one skilled in the art to generate and verify antibodies against any FGFR3 mutations, starting with the generation of antigen exemplified by the FGFR3 S371C mutation as disclosed in Example 2. Second, FGFR3 S371C mutation is recited in the Examples for producing antibodies. Thus, the Examiner's allegation that FGFR3 G380C is the only mutation disclosed in the application is clearly erroneous. Third, Examples 6, 10 and 13 demonstrate both the in vivo and in vitro functions of molecules of the present invention. Therefore, the enablement requirement is fulfilled and the rejection under 35 U.S.C. § 112, first paragraph, as lacking enabling disclosure should be withdrawn.

Claims 1, 4-6, 10, 15, 17 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by International patent application publication No. WO 00/68424 to Cappellen et al (referred to hereafter as "Cappellen"). Cappellen teaches methods of identifying FGFR3 mutation using PCR, RT-PCR or immunochemistry. Although Cappellen does mention using FGFR3 antibodies to detect FGFR3 levels in tissues, it never discloses antibodies with increased affinity for FGFR, which is recited in the present claims. As explained above, "increased affinities" is a specifically defined characteristics of molecules of the present invention, having a K_D of less than about 50 nM, preferably less than about 30 nM and more preferably less than about 10 nM. Therefore, Cappellen does not teach or suggest the present invention and the rejection over Cappellen should be withdrawn.

Claims 1, 4-6, 10, 15, 17 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by a publication by Johnston et al. (JBC, 270(51):30643-30650, 1995, referred to hereafter as "Johnston"), as evidenced by another publication by Chellaiah et al. (JBC, 274(49): 34785-34794, 1999, referred to hereafter as "Chellaiah"). Johnston teaches polyclonal FGFR3 antibodies that were raised against the Ig II extracellular domain of FGFR3 and specifically bind FGFR3 polypeptides that comprise this domain while Chellaiah shows that the Ig II extracellular domain of FGFR3 is required for FGF9 ligand binding specificity. However, there is no disclosure in Johnston regarding increased affinity of the antibodies, which is a main feature of the molecules of the present invention as recited in the present claims. Therefore, Johnston does not teach or suggest the present invention and the rejection over Johnston should be withdrawn.

Claims 1 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cappellen, in view of US Patent No. 5,843,450 to Dawson et al. (referred to hereafter as "Dawson"). As discussed above, Cappellen does not teach or suggest the present invention. Dawson teaches Hepatitis GB Virus (HGBV) synthetic peptides useful for a variety of diagnostic and therapeutic applications, as well as kits for using the HGBV nucleic acid or amino acid sequences and antibodies which specifically bind to HGBV. Since Dawson does not teach FGFR antibodies with increased affinity as recited in the present claims, it does not remedy the deficiencies of Cappellen. Combining these two references will only lead one of ordinary skill in the art to make kits with antibodies referred to in Cappellen, instead of the kits of the present invention. Therefore, the rejection is improper and should be withdrawn.

Claims 1 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnston in view of Dawson. For the same reasons articulated for the combination of Cappellen and Dawson, the combination of Johnston and Dawson does not render claims 1 and 31 obvious and the rejection should be withdrawn.

It is respectfully submitted that claims 18 and 20 should be examined together with claim 15 since they further limit the scope of claim 15. It is further understood that process claims 32-35 and 38-44 are currently withdrawn but they will be rejoined and allowed that when product claims 1 and 10, from which they ultimately depend, are allowed.

Accordingly, the entire application is now in condition for allowance, early notice of which would be appreciated. Should the Examiner not agree with the Applicants' position, then a personal or telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of the application.

Respectfully submitted,

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